The claim fee status is as follws:

☐ Large Entity
☒ Small Entity

		After Amdmt	Paid for at least	Fee due for	Fee code
	Independent Claims:	2	3	0	Lg =102 Sm =202
	Total Claims	3	20	0	Lg =103 Sm =203

Support for new claims 143-4 can be found, for example, in the discussion in Example 9 (previously number Example 34) of repeating the treatment until plaque was no longer observable. Support for the amendment can be found, for example, at 29:6-9.

The changes to the title and specification are intended to focus on disclosure relevant to the claimed embodiment.

Notice to Comply re Sequence Disclosure Requirements; Specification

As the aspect of the invention now claimed does not require the sequence information giving rise to the Notice to Comply, the sequences have been deleted. Accordingly, there no longer believed to be a sequence requirement applicable to this application.

Similarly, the requirement for SEQ ID numbers is also believed to no longer be applicable.

Claim Rejections - 35 U.S.C. §102/103(a)

Claim 142 stood rejected under 35 U.S.C. §102(b) or, in the alternative, under 35 U.S.C. §103(a), based on Hellgren et al., US Patent 4,963,491. Applicants respectfully traverse.

On the rejection for anticipation, the Applicants surmise that the rejection must be premised on principles of inherent anticipation, since a word search of the cited document confirms that not one word relates to any type of plaque. As discussed in M.P.E.P. §2112, such a

rejection requires that the element not expressly set forth in the reference necessarily flows from the disclosures of the reference. This requirement is not met here.

The '491 patent is in its core discussions is about cleaning wounds and objects such as textiles. One word in the specification mentions that teeth can be cleaned. There is no concrete exemplification from which to infer what type of teeth are to be treated, or even that teeth in situ are to be treated. Teeth cleaning occurs often without plaque being effectively removed, or without plaque being present. Thus, treating to effectively remove plaque, as claimed, does not necessarily follow from the brief mention of teeth cleaning in the '491 patent. Accordingly, the rejection under 35 U.S.C. §102 should be withdrawn.

On the rejection under 35 U.S.C. §103, Applicants respectfully submit that the disclosure that krill enzymes can be used to debride wounds or clean textiles does not render the claims obvious. While the results obtained in these contexts may be strong, nonetheless enzymes have been used in cleaning textiles for quite some time, and similarly there is a long history of use in wound debridement. Thus, effectiveness in a different, highly complex environment, namely dental plaque, would not have been apparent to one of ordinary skill.

The complexity of dental plaque is illustrated by the following discussion in US Patent 6,159,447 (a patent which relates to treating plaque with an anchored enzyme):

> Plaque is a heterogeneous mixture of bacterial aggregations embedded in a sticky matrix. While bacterial composition of plaque ranges from 50 to 70 percent, the matrix is derived from dead cells, salivary glycoproteins and serum proteins that are laid on a polysaccharide backbone. The bacteria synthesize the polysaccharides for the plaque backbone as a step in their own colonization process. In addition to the viable bacteria and the matrix, plaque also contains food debris, small numbers of epithelial cells, white blood cells and various other components which are derived from the host and the host's activities.
>
> The formation and development or proliferation of plaque occurs in two stages. The first step may require a base layer of salivary glycoproteins on the tooth's surface as well as on the soft tissue in the oral cavity. This base organic layer, derived from saliva, is adsorbed onto the surface and forms an acquired pellicle. This insoluble acquired pellicle serves as the foundation for supragingival plaque. The second step is the bacterial colonization

> by "pioneering" bacteria of the acquired pellicle. Once the bacteria have attached to the surface of a structure, they aggregate, develop colonies and plague begins to form.
>
> There are well over 100 different bacterial species in various dental plaques. This variation in the types of bacteria is influenced by diet, salivary components and bacterial interactions, to name a few. The location of the plaque in the oral cavity, the time of the day, age of the patient and the status of the general oral hygiene of the patient all contribute to the implications and consequences of dental plaque and periodontal disease. Consequently, it is not surprising that plaque is a heterogeneous collection of bacterial communities attached to the tooth providing a vast array of biochemical and physiological consequences. Two major pathological conditions as consequences are periodontal disease and dental caries.
>
> Enzymes as therapeutic agents present unique possibilities. However, some of the early oral pathology research using enzymes was based on the assumption that they would be bactericidal to colonies of organisms found in plaque and therefore would act as "disinfectants". This approach, however, was not fruitful. Recently, it was shown that treatment of buccal epithelial cells with protease altered bacterial adhesion; however, this treatment also distorted the ratios of various bacterial populations. More promising results were obtained when the focus was shifted from bactericidal action to altering plaque formation. These latter results were seen in vitro and in vivo as well as in animal models and humans in clinical trials. However, these approaches also fell short of desired therapeutic effectiveness most likely because the required time for an effective action exceeded the retention time of the enzyme in the oral cavity. In short, salivary flow, other fluid and food movement and normal mechanical agitation in the oral cavity reduced the retention time of the enzyme(s). These factors shortened the residence time of the enzymes, resulting in less than desirable clinical efficacy.

Thus, other enzymes have apparently failed in this context.

Applicant would respectfully submit that the fact that the type of enzyme mixture recited in the claims would be effective in removing plaque, as illustrated in Examples 8 and 9 (previously 33 and 34), was obvious only after the applicant presented the result.

Claim Rejections - 35 U.S.C. §103(a)

The prior claim also stood rejected under 35 U.S.C. §103 based on Karistam, EP 257 003 in view of Ratcliff, US 4,837,009. Applicant respectfully traverses.

Karistam is cited for substantially the same disclosure as is found in Hellgren, but perhaps further including the disclosure that krill enzymes include a hyaluronidase activity that degrades a glycoaminoglycan. Ratcliff is asserted in the Office Action to teach:

> that dental plaque is a complex extracellular matrix containing glucosaminoglycans, chondroitin sulfates, glycoproteins, and proteins. Ratcliff further teaches that degradation of these compounds retards plaque growth.

The Office Action cites for these propositions the following text italicized text from Ratcliff:

> *Bacterial agglutinigation includes the conversion of sucrose to glucans and fructans by enzymes known as glycosyltransferases. These enzymes are of bacterial origin. The plaque maas becomes a complex extra cellular (of microorganisms) matrix containing sulphated glucosamineglycans, proteoglycans, glycoproteins, sugar, proteins and lipids which aid in the process of bacterial agglutination.* These compounds include the presence of sulphur and become unstable in the presence of high oxygen compounds. The oxygen splits the sulphide bonds to form sulphates or SO_2.
>
> Clinical observations by the inventor have led to the conclusion that all of these biochemical compounds are attacked to a greater or lesser extent by stabilized chlorine dioxide. Since these compounds may be used as nutrients for bacteria, the reduction of the compounds will inhibit bacterial growth. *More specifically, the stabilized chlorine dioxide oxidizes carbohydrates, chondroitin sulphates, glucosaminglycans, glycoproteins, proteins and lipids. Since these compounds arise as bacterial by products and debris from dead and dying cells, are of salivary origin and are the mechanism of agglutination of the plaque mass, their degradation/oxidation retards plaque growth.*

Ratcliff at 3:62 – 4:22 (citation omitted).

Applicant would respectfully submit that Ratcliff indicates that stabilized chlorine dioxide attacks the complex mixture of components of plaque. The implication that because krill enzymes have at least some apparently appropriate classes of enzymes they would be effective in

the real world, is mistaken. Applicant respectfully submits that legal obviousness requires more than information that may pique the interest of a scientist, but information sufficient to conclude that there would be a reasonable expectation of success in conducting the claimed method.

Accordingly, Applicant respectfully submits that the rejection is in error, and should be withdrawn.

Conclusion

In light of the above discussion and amendments, it is respectfully submitted that the claims are in condition for allowance. The issuance of a Notice of Allowance is earnestly solicited.[2]

Respectfully submitted,

Arthur E. Jackson
Registration No. 34,354

Dechert
Princeton Pike Corporate Center
PO Box 5218
Princeton, New Jersey 08543-5218
Allen Bloom (609) 620-3214
Arthur E. Jackson (609) 620-3254
Fax: (609) 620-3259
Attention: Arthur E. Jackson

[2] **FEE DEFICIENCY**

IF ANY ADDITIONAL EXTENSION IS REQUIRED, PLEASE CONSIDER THIS PAPER A PETITION FOR SUCH AN EXTENSION; ANY FEE FOR THE EXTENSION REQUIRED FOR CONSIDERATION OF THIS PAPER BUT NOT ENUMERATED ABOVE OR IN A TRANSMITTAL OR OTHER ASSOCIATED PAPER CAN BE CHARGED TO ACCOUNT NO. 04-0480.

AND/OR

IF ANY ADDITIONAL FEE IS REQUIRED FOR CONSIDERATION OF THIS PAPER, PLEASE CHARGE ACCOUNT NO. 04-0480.

APPENDIX A1: PENDING CLAIMS (CLEAN COPY)

142. (**Amended**) A method of removing dental plaque in an animal subject comprising:

contacting the dental plaque with a dental plaque removing effective amount of a hydrolase mixture comprising enzymes from krill.

143. (**New**) A method of removing dental plaque comprising:

contacting the dental plaque, wherein the dental plaque is visually observable, with a dental plaque removing effective amount of a hydrolase mixture comprising enzymes from krill.

144. (**New**) The method of claim 143, wherein the contacting is conducted or repeated until dental plaque is not longer visually observable.

APPENDIX A2: CHANGES TO CLAIMS (REDLINE)

142. **(Amended)** A method of removing dental plaque <u>in an animal subject</u> comprising:

contacting the dental plaque with a dental plaque removing effective amount of a hydrolase mixture comprising enzymes from krill.

APPENDIX B1: REPLACEMENT PARAGRAPHS (CLEAN COPY)

At 2:3-28:

DELETE ALL

at 2:29 – 3:6:

DELETE ALL

at 3:7-9:

DELETE ALL

at 3:10 – 5:23, replace the text with the following:

The invention further provides (a) methods relating to certain conditions using effective amounts of the enzyme described above, (b) compositions for use in such methods, (c) pharmaceutical compositions containing effective amounts of enzyme for use in such methods, and (d) uses of the enzyme composition for manufacturing a medicament for use in such methods. The methods are for:

B1

(1) removing dental plaque, where preferably the amount of the multifunctional enzyme administered is a dental plaque removing effective amount.

The method comprises administering a composition comprising enzymes obtained from krill. The composition of the invention can also be used to remove dead of divergent cells.

at 5:23-25:

DELETE ALL

at 5:26 – 6:20:

DELETE ALL

APPENDIX B1: REPLACEMENT PARAGRAPHS (CLEAN COPY) – (continued)

at 6:21 – 9:12:

DELETE ALL

at 9:13 – 10:7:

DELETE ALL

at 10:8-17:

DELETE ALL

at 10:18-25:

DELETE ALL

at 10:26 – 11:4:

DELETE ALL

at 11:5-11:

DELETE ALL

at 11:12-15:

DELETE ALL

at 11:16-20:

DELETE ALL

APPENDIX B1: REPLACEMENT PARAGRAPHS (CLEAN COPY) – (continued)

at 11:21-30:

DELETE ALL

at 12:1-6:

DELETE ALL

at 12:7-11:

DELETE ALL

at 12:12-16:

DELETE ALL

at 12:17-18:

DELETE ALL

at 12:19-24:

DELETE ALL

at 35:22 – 40:39:

DELETE ALL

at 42:27 – 43:11, replace the text with the following:

BB

Samples of each preparation were analyzed by SDS-PAGE, and each preparation was found to contain a single protein that banded with apparent molecular weight of 29 kd. The SDS bands were electroblotted onto PVDF membranes and sequenced through 25 cycles of Edman

APPENDIX B1: REPLACEMENT PARAGRAPHS (CLEAN COPY) – (continued)

degradation. See, Matsudaira, J. Biol. Chem., 262: 10035-10038, 1987. Each preparation yielded the identical sequence. Accordingly, it is clear that all three preparations are homogenous, although each is micro-heterogeneous at position 5. The proteolytic activity of each of the three preparations was tested against substrate benzoyl-val-gly-arg-p-nitroaniline. Hydrolysis of this substrate can be monitored at 210 nm, reflecting the release of p-nitroaniline. The pH-dependence of the three preparations at an ionic strength of 0.1 M is shown in Fig. 9. The profile for Prep-3 (shown with filled squares), Prep-8 (shown with open diamonds) and Prep-11 (shown with filled diamonds) are identical. All three had a pH optimum for this substrate of 9.5.

at 51:11 – 52:10, replace the text with the following:

Example 4 - Timecourse of Cell Surface Recovery of Adhesion Molecules

DO-11.10 T cell hybrids (this cell line is described by Shimonkevitz et al., J. Experimental Med. 158: 303, 1983) were treated with 500 μg/ml of the krill-derived multifunctional hydrolase prepared according to Example 1B and tested for the CD4 marker as described in Example 3B. Immediately after the treatment, well less than 1% of the amount of CD4 found in the controls was found on the hydrolase-treated cells. 48 hours later, the levels in treated cells were the same as those in untreated cells.

Example 5 - Cell Binding Comparisons

The effectiveness of various members of the multifunctional enzyme family, i.e., the non-krill multifunctional enzymes having at least about 60% homology with the krill-derived hydrolase, are compared with that derived from krill using the HL60 binding assay of Example 3A.

at 53:32 – 69:24:

DELETE ALL

APPENDIX B1: REPLACEMENT PARAGRAPHS (CLEAN COPY) – (continued)

at 69:25, replace the text with the following:

Example 8 – Dental plaque in dogs

at 70:8, replace the text with the following:

Example 9 – Human dental plaque

at 70:23 – 79:22:

DELETE ALL

APPENDIX B2: REPLACEMENT PARAGRAPHS (REDLINE)

At 2:3-28:

DELETE ALL

at 2:29 – 3:6:

DELETE ALL

at 3:7-9:

DELETE ALL

at 3:10 – 5:23:

The invention further provides (a) methods relating to certain conditions using effective amounts of the enzyme described above, (b) compositions for use in such methods, (c) pharmaceutical compositions containing effective amounts of enzyme for use in such methods, and (d) uses of the enzyme composition for manufacturing a medicament for use in such methods. The methods are for:

~~(1) treating or prophylactically preventing a microbial infection [e.g. viral such as: a herpes (e.g. HSV-1, HSV-2, herpes zoster or genital herpes infection), HIV, hepatitis, influenza coronavirus, cytomegalovirus, rhinovirus or papilloma virus infection; an infection causing a gastrointestinal disease such as ulcer or diarrhoea; a fungal infection such as a systemic, skin, oral, vaginal or esophageal fungal, including, for example, yeast infection, including a fungal nail infection and candida infections; microbial infections of the eye, preferably treated with ocular administrations; bacterial infections including staphylococcus, streptococcus, klebsiella, pseudomonas, gonorrhea, haemophilus, chlamydia, syphilis and E. coli infections and bacterial infections causing chancroid; opportunistic microbial infections in immuno-compromised patients where~~

APPENDIX B2: REPLACEMENT PARAGRAPHS (REDLINE) – (continued)

~~preferably the administered amount of the multifunctional enzyme, described below, is a microbial infection treating or preventing effective amount or has inhibitory activity against cell-cell or cell-virus adhesion;~~

~~(2) treating or prophylactically preventing dermatological conditions, such as, for example, acne, psoriasis or eczema, including facial seborrheic eczema or eczema of the hands, face or neck, hemorrhoids and the like, where preferably the amount of the multifunctional enzyme administered is a dermatological condition treating or preventing effective amount;~~

~~(3) treating or prophylactically preventing cystic fibrosis, COPD, cancer, for example, by administering a tumor treating effective amount or a tumor metastasis preventing or inhibiting amount of enzyme, atherosclerosis, asthma, septic shock, toxic shock syndrome, tissue adhesions such as tendon sheath, abdominal post-surgical or joint adhesions, reperfusion injury, malaria, immune disorder such as an autoimmune disease, apoptosis, colitis and enteritis, such as Crohn's disease, where preferably the amount of the multifunctional enzyme administered is effective for treating or preventing;~~

~~(4) treating or prophylactically preventing wound infection (by applying to the wound a microbial infection preventing effective amount of the enzyme or by enhancing the healing of the wound by administering a microbe inhibiting effective amount of the enzyme), when treated the wound can be substantially free of necrotic tissue;~~

~~(5) treating or prophylactically preventing acute or chronic inflammation, where preferably the amount of the multifunctional enzyme administered is an acute or chronic inflammation treating or preventing effective amount;~~

APPENDIX B2: REPLACEMENT PARAGRAPHS (REDLINE) – (continued)

~~(6) treating or prophylactically preventing an indication selected from the group consisting of pain, bronchitis, haemophilus influenzae infections, mycoplasma in lungs, foreskin infections, athlete's foot, fistulae infections, infected topical ulcers, gastric ulcers, navel infections in newborns, wrinkles, polyps, scars and kelloids, lichen planus, boils, warts and allergic itch, prostatitis, mastitis, gingivitis, sinusitis, arthritis and inflamed joints, diarrhoea, eye disease, such as glaucoma or cataracts, and hair thinness, where preferably the amount of the multifunctional enzyme administered is a treating or preventing effective amount;~~

~~(7) removing dead or peeling skin from otherwise healthy skin to improve the skin's appearance, where preferably the amount of the multifunctional enzyme administered is a dead skin removing effective amount;~~

~~(8) lysing blood clots, where preferably the amount of the multifunctional enzyme administered is a clot lysing effective amount; and~~

~~(9)~~(1) removing dental plaque, where preferably the amount of the multifunctional enzyme administered is a dental plaque removing effective amount.

The method comprises administering a composition comprising ~~a the multifunctional enzyme described above~~**enzymes obtained from krill**. The composition of the invention can also be used to remove dead of divergent cells.

at 5:23-25:

DELETE ALL

at 5:26 – 6:20:
DELETE ALL

APPENDIX B2: REPLACEMENT PARAGRAPHS (REDLINE) – (continued)

at 6:21 – 9:12:
DELETE ALL

at 9:13 – 10:7:
DELETE ALL

at 10:8-17:
DELETE ALL

at 10:18-25:
DELETE ALL

at 10:26 – 11:4:
DELETE ALL

at 11:5-11:
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at 11:12-15:
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at 11:16-20:
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at 11:21-30:
DELETE ALL

at 12:1-6:

APPENDIX B2: REPLACEMENT PARAGRAPHS (REDLINE) – (continued)

DELETE ALL

at 12:7-11:
DELETE ALL

at 12:12-16:
DELETE ALL

at 12:17-18:
DELETE ALL

at 12:19-24:
DELETE ALL

at 35:22 – 40:39:
DELETE ALL

at 42:27 – 43:11:

Samples of each preparation were analyzed by SDS-PAGE, and each preparation was found to contain a single protein that banded with apparent molecular weight of 29 kd. The SDS bands were electroblotted onto PVDF membranes and sequenced through 25 cycles of Edman degradation. See, Matsudaira, J. Biol. Chem., 262: 10035-10038, 1987. Each preparation yielded the identical sequence: ~~I V G G M/N E V T P H A Y P W Q V G L F I D D M Y F~~. Accordingly, it is clear that all three preparations are homogenous, although each is micro-heterogeneous at position 5. The proteolytic activity of each of the three preparations was tested against substrate benzoyl-val-gly-arg-p-nitroaniline. Hydrolysis of this substrate can be monitored at 210 nm, reflecting the release of p-nitroaniline. The pH-dependence of the three preparations at an ionic strength of 0.1 M is shown in Fig. 9. The profile for Prep-3 (shown with

APPENDIX B2: REPLACEMENT PARAGRAPHS (REDLINE) – (continued)

filled squares), Prep-8 (shown with open diamonds) and Prep-11 (shown with filled diamonds) are identical. All three had a pH optimum for this substrate of 9.5.

at 51:11 – 52:10:

Example ~~3C~~4 - Timecourse of Cell Surface Recovery of Adhesion Molecules

DO-11.10 T cell hybrids (this cell line is described by Shimonkevitz et al., J. Experimental Med. 158: 303, 1983) were treated with 500 μg/ml of the krill-derived multifunctional hydrolase prepared according to Example 1B and tested for the CD4 marker as described in Example 3B. Immediately after the treatment, well less than 1% of the amount of CD4 found in the controls was found on the hydrolase-treated cells. 48 hours later, the levels in treated cells were the same as those in untreated cells.

Example ~~4~~5 - Cell Binding Comparisons

The effectiveness of various members of the multifunctional enzyme family, i.e., the non-krill multifunctional enzymes having at least about 60% homology with the krill-derived hydrolase, are compared with that derived from krill using the HL60 binding assay of Example 3A.

~~Example 5 - Mouse Ovarian Tumor Treatment~~

~~25,000 mouse ovarian tumor cells were injected into the abdominal cavity of 12 C3H/hsd mice). On days 1, 2 and each of days 5-9, 1 ml of either saline or 200 □g of krill multifunctional hydrolase (prepared as described in Example 1C) dissolved in saline was injected into the ascites. In Figure 4, weight gains (an indication of tumor growth) for saline treated (dark circles) and hydrolase treated (open circles) mice are shown. In Figure 5, the percentage of the animals surviving over time for saline (line A) and hydrolase (line B) treated mice. Solid tumors formed in the control mice, but not in the enzyme-treated mice.~~

~~Tumor cells were recoverable from the ascites fluid of the treated mice. 25,000 such recovered tumor cells were injected into each of 6 C3H/hsd mice. In control experiments, the same number of untreated mouse ovarian tumor cells were injected into C3H/hsd mice. Tumors formed in the control mice, but not in the mice injected with recovered cells.~~

APPENDIX B2: REPLACEMENT PARAGRAPHS (REDLINE) – (continued)

at 53:32 – 69:24:
DELETE ALL

at 69:25:
Example ~~338~~ 8 – Dental plaque in dogs

at 70:8:
Example ~~339~~ 9 – Human dental plaque

at 70:23 – 79:22:
DELETE ALL